



UNDERSTANDING AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases are a relatively new category of diseases that are different from autoimmune diseases. However, autoimmune and autoinflammatory diseases share common characteristics in that both groups of disorders result from the immune system attacking the body's own tissues, and also result in increased inflammation. This overview contains general information on the immune system, and provides brief descriptions of some of the more common autoinflammatory diseases.

THE IMMUNE SYSTEM

When your body is attacked—perhaps by a virus or other germs—your immune system defends you. It “sees” and kills the germs that might hurt you.

But when the system doesn't work right, this process can cause harm. Immune cells can mistake your body's own cells as invaders and attack them. This “friendly fire” can affect almost any part of the body. It can sometimes affect many parts of the body at once. This is called “autoimmunity” (meaning “self-immunity”).

The part of the immune system that orchestrates all of this develops as a person grows, and is known as the **acquired** immune system. It “remembers”

foreign antigens, or proteins, so that it can fight them if they come back. It employs white blood cells called lymphocytes.

But the body also has an **innate** (inborn) immune system that is more primitive. It employs types of white blood cells called granulocytes and monocytes to destroy harmful substances. In **autoinflammatory** diseases, this innate immune system causes inflammation for unknown reasons. It reacts, even though it has never encountered autoantibodies or antigens in the body.

Autoinflammatory disorders are characterized by intense episodes of inflammation that result in such symptoms as fever, rash, or joint swelling. These diseases also carry the risk of amyloidosis, a potentially fatal buildup of a blood protein in vital organs.

There are several different types of autoinflammatory diseases.

FAMILIAL MEDITERRANEAN FEVER (FMF)

People with familial Mediterranean fever (FMF) suffer from recurring bouts of fever, most commonly with severe abdominal pain due to inflammation of the abdominal cavity (peritonitis). Attacks can also include arthritis (painful, swollen joints), chest pain from inflammation of the lung cavity (pleurisy), and skin rashes.

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The mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the U.S. Department of Health and Human Services' National Institutes of Health (NIH), is to support research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of basic and clinical

scientists to carry out this research; and the dissemination of information on research progress in these diseases. For more information about the NIAMS, call the information clearinghouse toll free at 301-495-4484 or 877-22- NIAMS or visit the NIAMS website at www.niams.nih.gov.

FMF usually begins in childhood and occurs most commonly in people of Jewish, Armenian, Arab, and Turkish backgrounds living in the United States and abroad. As many as 1 in 200 people in these populations have the disease, and as many as 1 in 5 to 1 in 7 carry a mutated *FMF* gene. The gene holds the code for making a protein known as pyrin. The pyrin protein, named from the Greek word for *fire*, bears a strong resemblance to several proteins found in the nucleus of cells. Some of these proteins are known to regulate inflammation. Usually a person must inherit two mutated copies of the gene—one from each parent—to get FMF. However, recent studies have shown that under some circumstances, one copy is enough to cause disease.

Colchicine—a medication commonly used to treat gout (a form of arthritis)—has been used successfully as a treatment for FMF. Colchicine reduces inflammation throughout the body.

NEONATAL ONSET MULTISYSTEM INFLAMMATORY DISEASE (NOMID)

Neonatal onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome, affects numerous organs and body systems, including the skin, joints, eyes, and central nervous system. For most children, the first sign of the disease is a rash that develops within the first 6 weeks of life. Other problems, including fever, meningitis, joint damage, vision and hearing loss, and mental retardation, can follow. The disease is progressive and often fatal. As many as 20 percent of children with NOMID don't survive to adulthood.

Although the mechanism of NOMID is not completely understood, research has revealed mutations in a gene called *LNRP3* (formerly known as *CIAS1*) in approximately 60 percent of patients with the disease. A person only needs to have one abnormal copy of the gene to get the disease. *LNRP3* encodes cryopyrin and belongs to a group of interacting proteins involved in regulating inflammation and programmed cell death, which plays a crucial role in ridding the body of cells that are no longer needed. The mutations, scientists have found, lead to an

imbalance of a cytokine, or chemical messenger, called interleukin-1 (IL-1), which is believed to drive the increased inflammation that causes damage in patients with the disease.

People with NOMID usually respond well to anakinra, a drug that blocks IL-1 action and is sometimes used for rheumatoid arthritis. Anakinra results in marked improvement both in symptoms and the inflammation underlying the disease.

TUMOR NECROSIS FACTOR (TNF) RECEPTOR-ASSOCIATED PERIODIC SYNDROME (TRAPS)

TRAPS (TNF receptor-associated periodic syndrome), formerly known as familial Hibernian fever, is characterized by long, dramatic, episodes of high fever; severe pain in the abdomen, chest, or joints; skin rash; and inflammation in or around the eyes. The age of onset varies from early childhood to adulthood, and the disease appears to affect men and women equally. The earliest cases of TRAPS were reported in individuals of Irish-Scottish descent, but the disease has since been found in nearly all ethnic groups.

TRAPS is caused by a genetic defect in a protein known as tumor necrosis factor receptor (TNFR). TNFR sits on the surface of cells and binds to tumor necrosis factor (TNF), a protein that causes inflammation. Mutant TNFR promotes inflammation without TNF. A person only needs one abnormal copy of the gene to get the disease. Episodes can be triggered by infection or stress. Although a definitive treatment for TRAPS has yet to be identified, drugs known as TNF inhibitors are sometimes successful in treating the disease.

DEFICIENCY OF THE INTERLEUKIN-1 RECEPTOR ANTAGONIST (DIRA)

Deficiency of the interleukin-1 (IL-1) receptor antagonist (DIRA) is a newly discovered autoinflammatory disease. Children with the disorder display a constellation of serious and potentially fatal symptoms that include swelling of bone tissue; bone pain and deformity; inflammation of the periosteum (a layer of connective tissue around bone); and a rash

that can span from small individual pustules to extensive pustulosis that covers most of the patient's body. Most of the children begin to have symptoms from birth to 2 weeks of age.

Children with DIRA have inherited mutations in *IL1RN*, a gene that encodes a protein known as IL-1 receptor antagonist (IL-1Ra). IL-1Ra binds to the same cell receptors as the inflammatory protein IL-1, and blocks its inflammatory actions. Without IL-1Ra, the children's bodies cannot control systemic inflammation that can be caused by IL-1. Although mutations that cause DIRA are rare, as many as 2.5 percent of the population of northwest Puerto Rico are carriers. Since DIRA is recessively inherited, these data suggest that it may be present in about 1 in 6,300 births in this population. Mutations may also be more common in individuals of Dutch descent.

Most patients with DIRA respond well to anakinra, the same drug previously mentioned for NOMID treatment, a synthetic form of human IL-1Ra.

BEHÇET'S DISEASE

Behçet's disease causes canker sores or ulcers in the mouth and on the genitals and inflammation in parts of the eye. In some people, the disease also results in arthritis, skin problems, and inflammation of the digestive tract, brain, and spinal cord.

Behçet's disease is common in the Middle East, Asia, and Japan; it is rare in the United States. In Middle Eastern and Asian countries, the disorder affects more men than women. In the United States, the opposite is true. Behçet's disease tends to develop in people in their twenties or thirties, but people of all ages can develop it.

The exact cause of Behçet's disease is unknown. Most symptoms of the disorder are caused by inflammation of the blood vessels. Doctors think that an autoinflammatory reaction may cause the blood vessels to become inflamed, but they do not know what triggers this reaction. Corticosteroids and immunosuppressive drugs are commonly used to treat the disease.

PROGRESS AND PROMISE

Further research should continue to enhance the understanding of the genetics and causes of autoinflammatory disorders, and result in improvements in diagnosing and treating these diseases. For information on autoinflammatory diseases that are supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), visit: www.niams.nih.gov/research/Ongoing_Research/Branch_Lab/Clinical_Director. For a listing of federally and privately supported clinical trials for a variety of autoinflammatory disorders, visit www.clinicaltrials.gov.

KEY WORDS

Acquired immune system. The part of the immune system that develops as a person grows. It employs antibodies to fight harmful substances.

Amyloidosis. A potentially fatal build up of a blood protein in vital organs.

Anakinra. An anti-inflammatory medication that is sometimes used for rheumatoid arthritis.

Antibody. A special protein produced by the body's immune system that recognizes and helps fight infectious agents and other foreign substances that invade the body.

Antigen. A foreign substance that triggers the production of antibodies when it is introduced into the body.

Autoantibody. An antibody that attaches to the body's own healthy tissues by mistake and signals the body to destroy them.

Autoimmune disease. A disease that results when the immune system mistakenly attacks the body's own tissues.

Autoinflammatory disease. A disease that results when the innate immune system causes inflammation for unknown reasons.

Behçet's disease. An autoinflammatory disease that causes canker sores or ulcers in the mouth and on the genitals and inflammation in parts of the eye.

Colchicine. An anti-inflammatory medication commonly used to treat gout.

Cryopyrin. A protein involved in regulating inflammation and programmed cell death.

Deficiency of the interleukin-1 receptor antagonist (DIRA). An autoinflammatory disease caused by a deficiency of the protein interleukin-1 receptor antagonist.

Familial Mediterranean fever (FMF). An autoinflammatory disease characterized by a mutation in the gene that codes for pyrin.

Immune system. A complex network of specialized cells and organs that work together to defend the body against attacks by foreign invaders, such as bacteria and viruses.

Innate immune system. The part of the immune system that is more primitive. It employs types of white blood cells called granulocytes and monocytes to destroy harmful substances.

Neonatal onset multisystem inflammatory disease (NOMID). An autoinflammatory disease associated with a mutation in the gene *CIAS1*.

Pyrin. A protein involved in regulating inflammation.

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS). An autoinflammatory disorder caused by a genetic defect in a protein known as tumor necrosis factor receptor (TNFR).

The National Institutes of Health (NIH)—The Nation's Medical Research Agency—includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. It is the primary Federal agency for conducting and supporting basic, clinical, and translational medical research, and it investigates the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

NIH Publication No. 10–7576

FOR YOUR INFORMATION

This publication contains information about medications used to treat the health condition discussed here. When this publication was printed, we included the most up-to-date (accurate) information available. Occasionally, new information on medication is released.

For updates and for any questions about any medications you are taking, please contact the U.S. Food and Drug Administration toll free at 888-INFO-FDA (888-463-6332) or visit its website at www.fda.gov.

For updates and questions about statistics, please contact the Centers for Disease Control and Prevention's National Center for Health Statistics toll free at 800-232-4636 or visit its website at www.cdc.gov/nchs.